REMARKS

Amendment

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Double Patenting

Claims 1, 2, 5, 6, 8, 12 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent 6,210,946. Applicants will submit a terminal disclaimer to obviate the double patenting rejection, when allowable subject matter is obtained.

The 35 U.S.C. §101 Rejection

Claim 7 was rejected under 35 U.S.C. §101 as claiming the same invention as that of claim 1 of U.S. Patent 6,210,946. The rejection is moot because claim 7 has been canceled.

The 35 U.S.C. §112 Rejection

Claims 1-12 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The Examiner argued that a person having ordinary skill in this art would have to unduly experiment to practice the claimed invention. Applicants respectfully disagree.

Although the primary amino acid sequences of fiber proteins of various human and animal adenoviruses are highly diverse, the overall structural and functional organization of these proteins demonstrate remarkable degree of similarity. Indeed, all key features of the domains of the fiber proteins, i.e., the presence of the nuclear localization signal and the penton base binding site within the fiber tail, the presence of pseudorepeats in the shaft, the propeller-like structure of the knob, and trimeric configuration of the entire fiber molecule are highly conserved between various adenovirus serotypes. This overall structural and functional similarity has been exploited by investigators to successfully replace all or part of the fiber protein of one adenovirus serotype with those derived from another adenovirus serotype.

In contrast to the fiber domain shuffling research described above, the present invention discloses a method of creating a recombinant virion that lacks endogenous fiber tropism and possesses a novel tropism by splitting the functions of trimerization and ligand binding normally performed by the knob domain between two different protein moieties which would replace the fiber. This was achieved by replacing the fiber with an external trimerization motif to maintain the trimerization of the knobless fiber, and simultaneously introducing into the fiber a ligand capable of targeting the virion to a novel receptor. Since the role of the fiber is presumably to place the cell-binding site away from the surface of the virion, the fiber may be replaced with another rod-like trimeric protein. In addition to being trimeric, the replacement protein should have the ability to associate with the penton base of adenovirus and be incorporated into the virion. To prevent problems of incompatibility, the amino-terminus of the chimeric replacement protein was incorporated into the tail domain of the adenovirus fiber that attaches to the penton base.

As an example, the shaft of the fiber was replaced with the α-helical portion of the T4 fibritin protein in the present invention. In contrast to the fiber shaft, which is a triple β-spiral held

together with intra- and inter-chain hydrogen bonding, the α-helical segment of the fibritin is a parallel triple coiled-coil stabilized by inter-chain hydrophobic and ionic interactions. Thus, the Applicants have demonstrated the feasibility and utility of replacing the fiber protein with another rod-like trimeric protein composed of different structural units. Other trimeric proteins that can be used in the replacement protein have been disclosed in the specification and in the claims. In fact, a person having ordinary skill in this art would be able to construct an artificial protein having a coiled-coil secondary structure as a replacement protein.

Applicants submit that the scope of the claims 1-12 in the instant application has a reasonable correlation to the scope of the enablement provided. Accordingly, Applicants respectfully request that the rejection of claims 1-12 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 13-15 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The Examiner argued that the nature of the invention is gene therapy which is not well developed and unpredictable.

However, Applicants submit that the present invention makes no claim to any of the unpredictable features of gene therapy cited by the Examiner such as the fate of the expression vectors *in vivo*, or processing and expression of exogenous protein *in vivo*. The present invention is drawn to the making and uses of recombinant adenoviruses that do not bind to the cognate cell surface receptor, the coxsackie-adenovirus receptor (CAR), but instead possess novel tropism. No undue experimentation is required to put a therapeutic gene into the genome of the adenovirus as claimed in claim 13 since one of skill in the art routinely replaces marker genes in vector constructs with other genes of interest.

The method of killing tumor cell using herpes simplex virus thymidine kinase (HSV-TK) and ganciclovir recited in claim 15 is also well known to one of skill in the art. The HSV-TK/ganciclovir cytotoxic method is currently included in a number of gene therapy protocols and clinical trials. Applicants submit that using the adenovirus of the present invention in the HSV-TK/ganciclovir method is an improvement of these prior art methods because of the enhanced targeting capability of the claimed adenovirus. Hence, Applicants submit that no undue experimentation is required to practice claims 13-15 using the claimed adenovirus of the present

invention. Accordingly, Applicants respectfully request that the rejection of claims 13-15 under 35 U.S.C. §112, first paragraph, be withdrawn.

This is intended to be a complete response to the Office Action mailed September 19, 2001. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 7 has been canceled.